modified release formation having both immediate and sustained release properties. New claims 33-55 are directed to the modified release formulation of original claims 12-32, while the sustained release claims have been canceled to facilitate prosecution without prejudice to Applicants' ability to pursue them separately in a continuation application. No new matter is believed to be introduced by this amendment. The upper limit in newly added claim 33 of about 6.8:1 for the ratio of hydrophilic polymer of water-insoluble polymer is supported by the specification at page 11, lines 23-25, which shows a preferred embodiment with a weight ratio that calculates to be 6.8:1 including the hydrophilic polymer in the guaifenesin DC. The range of values in newly added claim 43 for the ratio of first and second portions of guaifenesin is supported by the specification, see Examples 4 and 5. The ranges of component weight percents in newly added claim 55 are supported by the specification as they represent the ranges demonstrated by the Examples including the subcomponents of "guaifenesin DC" as defined in the specification at page 11, lines 8-9.

Original claims 1-32 were rejected under 35 U.S.C. § 103(a) as unpatentable over Drost et al., U.S. Patent No. 4,756,911, in view of Dansereau et al., U.S. Patent No. 5,032,406. To the extent that the Examiner has applied these references to original claims 12-32 and to the extent arguably applicable to newly added claims 33-55, Applicants respectfully traverse this rejection.

Drost et al. does not teach or suggest the invention as presently claimed. Drost et al. does not disclose a pharmaceutical composition containing guaifenesin or its therapeutic category, which is expectorant -- not bronchodialator. Drost et al. does not disclose a composition having both an immediate release portion that is fully bioavailable in the subject's stomach and a sustained release portion that provides therapeutically effective bioavailability for at least 12 hours. Moreover, Drost et al. does not disclose or suggest the use of a water-insoluble polymer, e.g., an acrylic resin, in such a modified release tablet.

Dansereau et al. does not supply the deficiencies of Drost et al. While Dansereau et al. does disclose two separate guaifenesin portions with different release characteristics, this disclosure describes a dual-action tablet that includes an outer portion that slowly releases a first dose of the drug and an inner portion that provides a second dose which is delayed until some time after administration, i.e., until the outer portion is dissolved sufficiently to expose the inner portion to gastric fluids. Such an approach is totally different from that of the claimed invention.

In fact, Dansereau et al. specifically teaches away from employing any immediate release portion: "This dual-action tablet is contrasted with repeat-action tablets which give an immediate dose followed by a sustained dose" (col. 2, lines 37-39) (emphasis added). Moreover, the inner dose of Dansereau et al. is not "fully bioavailable in the subject's stomach" because of the time delay caused by the slow-release outer portion.

The Examiner has not pointed to any suggestion in the references cited or the art to combine the teachings of Drost et al. and Dansereau et al. In fact, these references present alternative approaches to providing long acting drug administration and as such would not be combined. Even if it were proper to combine the teachings of Drost et al. and Dansereau et al., the resulting combination would not disclose or suggest the claimed invention. At best, such a combination would suggest only that Dansereau et al.'s outer portion might employ the release chemistry of Drost et al.'s composition. This combination falls woefully short of suggesting the claimed invention since it is still "inside out" from a functional standpoint, i.e., has no immediate release portion.

CONCLUSION

Applicants maintain that this application is in condition for allowance, and such disposition is earnestly solicited. If the Examiner believes that an interview with Applicants' representative, either by telephone or in person, would further prosecution of this application, we would welcome the opportunity for such an interview.

Respectfully submitted,

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APPENDIX A

VERSION OF CLAIMS WITH MARKINGS

Please cancel claims 1-32 and add the following new claims 33-55 provided in a a marked version format in accordance with 37 C.F.R. § 1.121(b) as follows:

33. A modified release tablet having two portions, wherein a first portion comprises a first quantity of guaifenesin in an immediate release form which becomes fully bioavailable in the subject's stomach and a second portion comprises a second quantity of guaifenesin and a release-delaying matrix comprising a hydrophilic polymer and a water-insoluble polymer wherein the weight ratio of said hydrophilic polymer to said water-insoluble polymer is in the range of from about 1:1 to about 6.8:1, wherein said tablet demonstrates a C_{max} equivalent to an immediate release guaifenesin product and wherein said tablet also provides therapeutically effective bioavailability for at least twelve hours after dosing in a human subject according to serum analysis.

34. The modified release tablet of claim 33 wherein said hydrophilic polymer is selected from the group consisting of acacia, gum tragacanth, locust bean gum, guar gum, karaya gum, modified cellulosic, methylcellulose, hydroxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, carboxymethylcellulose, agar, pectin, carrageen, alginate, carboxypolymethylene, gelatin, casein, zein, bentonite, magnesium aluminum silicate, polysaccharide, modified starch derivatives, and a combination thereof.

35. The modified release tablet of claim 33 wherein the water-insoluble polymer is selected from the group consisting of polyacrylic acids, acrylic resins, acrylic latex dispersions, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and a combination thereof.

36. The modified release tablet of claim 33 wherein said hydrophilic polymer is hydroxypropyl methylcellulose and said water-insoluble polymer is an acrylic resin.

37. The modified release tablet of claim 33 wherein said tablet additionally comprises an additive selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate, powdered stearic acid, hydrogenated vegetable oils, talc, polyethylene glycol, mineral oil, EMERALD GREEN LAKE, an FD&C color, sucrose, lactose, gelatin, starch paste, acacia, tragacanth, povidone, polyethylene glycol, Pullulan, corn syrup, colloidal silicon dioxide, talc, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, triethanolamine, polyoxyethylene sorbitan,

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poloxalkol, quarternary ammonium salts, mannitol, glucose, fructose, xylose, galactose, maltose, xylitol, sorbitol, potassium chloride, potassium sulfate, potassium phosphate, sodium chloride, sodium sulfate, sodium phosphate, magnesium chloride, magnesium sulfate, magnesium phosphate, microcrystalline cellulose, sodium starch glycolate, and a combination thereof.

38. The modified release tablet of claim 33 wherein said first portion includes microcrystalline cellulose, sodium starch glycolate and magnesium stearate.

39. The modified release tablet of claim 33 wherein the total quantity of guaifenesin is from about 600 mg to about 1200 mg.

40. The modified release tablet of claim 33 wherein the total quantity of guaifenesin is 600 mg.

41. The modified release tablet of claim 33 wherein the total quantity of guaifenesin is 1200 mg.

42. The modified release tablet of claim 39 wherein the C_{max}, AUC_{inf} and AUC_{0-12} are approximately proportional to dosage strength.

43. The modified release tablet of claim 33 or 39 wherein the ratio of said first quantity of guaifenesin to said second quantity of guaifenesin is about 1:1 to about 5:1.

44. The modified release tablet of claim 33 or 39 wherein the ratio of said first quantity of guaifenesin to said quantity of second quantity of guaifenesin is about 5:1.

45. The modified release tablet of claim 41 wherein the C_{max} of said tablet is from about 1600 to 2500 μg/mL and said tablet has an AUC_{inf} of from about 5600 to 8750 hr*μg/mL.

46. The modified release tablet of claim 44 wherein the C_{max} of said tablet is at least 1900 μg/mL and said tablet has an AUC_{inf} of at least 7000 hr*μg/mL.

47. The modified release tablet of claim 40 wherein the C_{max} of said tablet is from about 800 to 1250 μg/mL and said tablet has an AUC_{inf} of from about 2800 to 4375 hr*μg/mL.

48. The modified release tablet of claim 47 wherein the C_{max} of said tablet is at least 1000 μg/mL and said tablet has an AUC_{inf} of at least 3500 hr*μg/mL.

49. The modified release tablet of claim 33 wherein said tablet has a half life, according to serum analysis, of at least 3 hours.

50. The modified release tablet of claim 33 wherein the second portion comprises about 95.5% by weight of guaifenesin DC, about 2.4% by weight of hydrophilic polymer and about 1.2% by weight of water-insoluble polymer.

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51. The modified release tablet of claim 33 wherein said first and second portions each comprise abutting substantially planar layers which form a bilayer tablet.

52. The modified release tablet of claim 33 wherein said first portion is provided as a coating on said second portion.

53. The modified release tablet of claim 33 which is approximately equally effective when administered to a patient on an empty or full stomach.

54. The modified release tablet of claim 41 which has the serum guaifenesin concentration profile of Figure 10.

55. The modified release tablet of claim 41 wherein the second portion comprises from about 85.5% to about 91.4% by weight of guaifenesin, from about 6.8% to about 10.1% by weight to hydroxypropyl methylcellulose, and from about 1.1% to about 2.9% by weight of an acrylic resin.

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